The impact of tamsulosin on cognition in Alzheimer disease with benign prostate hyperplasia

A study using the Hallym Smart Clinical Data Warehouse

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Abstract

Studies suggest that the use of alpha-blockers increases the risk of dementia in patients with benign prostate hyperplasia (BPH). Due to study limitations, the relationship between the use of alpha-blockers, such as tamsulosin, and the risk of dementia is still unclear. However, alpha1-adrenoreceptors are also present in the brain, so there is potential for adverse effects on cognitive function. Therefore, we investigated possible associations between the use of alpha-blockers and aggravation of cognitive decline in dementia patients using a clinical data analytic solution called the Smart Clinical Data Warehouse (CDW).

We retrospectively investigated clinical data using the Smart CDW of Hallym University Medical Center from 2009 to 2019. We enrolled patients with probable Alzheimer disease (AD) who had completed the Mini-Mental State Examination (MMSE) at least twice during follow-up, and who had BPH. We compared the difference in MMSE scores between patients who took tamsulosin for >1000 days and those who did not take any alpha-blocker. We tested the effect of tamsulosin on cognitive decline in patients with AD, using propensity score-matched logistic regression analysis.

Eligible cases were included in the tamsulosin (n=68) or no-medication (n=153) groups. After propensity score matching, clinical characteristics such as educational attainment and vascular risk factors were similar in the tamsulosin and no-medication groups. The MMSE scores did not differ significantly between the tamsulosin and no-medication groups (P=.470).

The results suggest that tamsulosin for BPH is not associated with worsening of the cognitive decline in patients with AD.

Abbreviations: 5-HT\textsubscript{1A} = serotonergic, AChEi = acetylcholine-esterase inhibitors, AD = Alzheimer disease, APOE = apolipoprotein E, BBB = blood-brain barrier, BMI = body mass index, BPH = benign prostate hyperplasia, CDW = Clinical Data Warehouse, D\textsubscript{3} = dopaminergic, DM = diabetes, EMR = electronic medical record, HUMC = Hallym University Medical Center, ICD = International Statistical Classification of Diseases and Related Health Problems, MMSE = Mini-Mental State Examination.

Keywords: Alzheimer disease, benign prostate hyperplasia, cognition, dementia, tamsulosin

1. Introduction

Benign prostate hyperplasia (BPH) is a common age-dependent disease affecting over half of men 65 years or older. Urology guidelines recommend alpha-blockers for the primary treatment of BPH.\textsuperscript{1,2} Molecular studies have identified 3 \(\alpha\)-adrenergic receptor subtypes (\(\alpha_{1A}, \alpha_{1B}, \alpha_{1D}\)). Of these, \(\alpha_{1A}\) is the most abundant receptor subtype in the human prostate.\textsuperscript{3,4} All \(\alpha\)-adrenergic receptor subtypes are also present in the brain, with
different distributions and localization. In particular, $\alpha_{1A}$ is more abundant in the hippocampus and hindbrain compared with $\alpha_{1B}$; therefore, there is a potential risk of adverse effects on cognitive function.\(^{[6-9]}\)

Tamsulosin is the most widely used $\alpha_1$-adrenergic receptor antagonist. Unlike other $\alpha_1$-adrenergic receptor antagonists, tamsulosin is 10- to 38-fold more selective for $\alpha_{1A}$ versus the $\alpha_{1B}$ subtypes.\(^{[10]}\) Radio-ligand assay studies have reported that tamsulosin has a binding affinity comparable to its $\alpha_{1A}$ affinity for dopaminergic (D3) and serotonergic (5-HT1A) receptors.\(^{[11]}\) Since tamsulosin has a strong affinity for all neurotransmitter receptors ($\alpha_{1A}$-adrenergic, dopaminergic, and serotonergic) that regulate and modulate important central nervous system functions, including mood, affect, attention, learning, and memory, previous investigators hypothesized that tamsulosin may increase the risk of developing dementia.\(^{[12,13]}\)

One study reported an association between the prescription of tamsulosin and a new diagnosis of dementia, such as Alzheimer disease (AD).\(^{[13]}\) However, data regarding the association between tamsulosin and dementia are conflicting,\(^{[14]}\) and clinical researchers have pointed out limitations of the original study.\(^{[15,16]}\)

The pathophysiology of AD is thought to begin many years before a diagnosis of AD dementia. There is a postulated temporal lag of at least 10 years between the deposition of A\(_\beta\) and the clinical syndrome of AD dementia.\(^{[17]}\) The associations observed in previous studies were over a median time of <5 years (19.8 vs 56.43 months), which is too short to cause dementia.\(^{[13,14]}\) Due to inevitable limitations of clinical studies, the relationship between the use of tamsulosin and risk of dementia remains unclear.

Therefore, we investigated possible associations between the use of tamsulosin and cognitive decline in patients with AD using the Smart Clinical Data Warehouse (CDW) over a period of 10 years.

### 2. Patients and methods

#### 2.1. Study population and design

We retrospectively investigated clinical data using the clinical big data analytic solution Smart CDW from Hallym University Medical Center (HUMC) from 2009 to 2019. The Smart CDW is based on the QlikView Elite Solution and is used at the 5 HUMC hospitals. It offers electronic medical record (EMR) text data analysis and integrated analysis of fixed data. Using the Smart CDW, we collected clinical data for patients with probable AD who had completed the Mini-Mental State Examination (MMSE) at least twice during follow-up and had BPH, some of whom were taking alpha-blockers, including tamsulosin, at Chuncheon Sacred Heart Hospital from January 2009 to June 2019. This study was approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University.

Dementia was defined based on the presence of ICD (International Statistical Classification of Diseases and Related Health Problems) -10 diagnostic codes for AD and 1 prescription filled for dementia medications (ie, donepezil, rivastigmine, galantamine, or memantine). The study enrolled subjects with dementia defined as having mild to moderate AD (MMSE 10–26, Clinical Dementia Rating 1–2). Of these, the tamsulosin group included males with BPH who had filled prescriptions for tamsulosin. Only patients who had taken tamsulosin for >1000 days and who had undergone MMSE testing >1000 days apart were included in the tamsulosin group. Only males with mild or moderate AD who had undergone MMSE testing >1000 days apart and those who did not take any alpha-blocker, including tamsulosin, were included in the no-medication group. We tested the effect of tamsulosin on cognition in mild to moderate AD using propensity score-matched logistic regression analysis. To evaluate the degree of cognitive decline, we retrospectively examined the total MMSE scores at initial and final follow-up. We compared the differences in MMSE scores between patients who took tamsulosin for >1000 days and those who did not take any alpha-blocker, including tamsulosin.

Clinical data and medical records were analyzed, and patients were excluded if they had a past or present central nervous system disease, hearing loss, or depression based on a diagnosis and subsequent treatment in the appropriate department. We collected clinical information on the patients' maximum duration of formal education, age, body mass index (BMI), and history of smoking. Information on vascular risk factors such as hypertension, type 2 diabetes mellitus (DM), hypercholesterolemia, and cardiovascular disease, defined as a diagnosis and subsequent treatment by a physician for the respective condition, was included.

#### 2.2. Propensity score matching and statistical analysis

After confirming normality, $\chi^2$ and Student $t$ tests were used to compare nominal and continuous variables, respectively. Since the use of tamsulosin was not randomized in the patient group, potential confounding and selection biases were accounted for using the propensity score. A propensity score for tamsulosin use was calculated from a logistic equation for each patient. The variables listed in Table 1 were included as covariates. The propensity score for tamsulosin use ranged from 0.05 to 0.83, and, in effect, represented the probability that a patient would use tamsulosin. We sought to match each tamsulosin user to a non-tamsulosin-using patient who had a similar propensity score, in a 1:1 ratio. Propensity score matching used the macro function of SPSS (SPSS Inc, Chicago, IL). The standardized difference was measured using the Practical Meta-Analysis Effect Size Calculator. All analyses were performed using Statistical Packages for the Social Sciences for Windows ver. 22.0 (IBM Corp, Armonk, NY); $P$ values $<.05$ were considered statistically significant.

### 3. Results

#### 3.1. Subject characteristics

All inclusion and exclusion criteria were met by 492 men with AD and BPH. The final subjects were placed in tamsulosin ($n=68$) and no-medication ($n=153$) groups. There were differences in age, BMI, and presence of hypertension and cardiovascular disease between the 2 groups. After propensity score matching, each group had 68 subjects. After matching, there were no significant differences in the measured clinical characteristics, and the standardized differences of all covariates, excluding hyperlipidemia, decreased. Thus, there were no significant differences in educational attainment, BMI, smoking, and vascular risk factors such as the proportions with hypertension, DM, hyperlipidemia, or cardiovascular disease across the study groups. The mean daily doses of acetylcholine-esterase inhibitors (AChEI) and memantine during the entire follow-up period were not significantly different (Table 1).
3.2. Differences in cognitive decline between the tamsulosin and no-medication groups in patients with AD

The initial and final MMSE scores in the tamsulosin group were 19.6 ± 5.9 and 16.9 ± 7.3, respectively; those for the no-medication group were 19.0 ± 5.8 and 15.4 ± 7.1. The differences in MMSE scores did not differ significantly (P = .470) between the tamsulosin and no-medication groups (Fig. 1). The mean interval for MMSE testing between the tamsulosin and no-medication groups was not significantly different (1341.2 ± 165.4 vs 1362.0 ± 231.9 days) (Table 2).

4. Discussion

This study examined possible associations between the use of tamsulosin, as treatment for BPH, and cognitive decline in males with mild to moderate AD. After propensity score matching, the clinical characteristics, including demographics and vascular risk factors, were very similar between the tamsulosin and no-medication groups. The baseline and follow-up MMSE scores after >1000 days did not differ significantly between the 2 groups. Thus, there was no significant difference in cognitive decline between the tamsulosin and no-medication groups in mild to moderate AD in this study.

### Table 1

Subject characteristics in the 2 diagnostic groups before and after matching.

<table>
<thead>
<tr>
<th></th>
<th>Before matching</th>
<th>After matching</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No-med. group</td>
<td>Tamsulosin group</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>70.3 (10.1)</td>
<td>73.2 (10.1)</td>
</tr>
<tr>
<td>Education, y (SD)</td>
<td>9.1 (4.6)</td>
<td>8.7 (4.9)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>18.6 (8.8)</td>
<td>21.3 (5.5)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>34 (22.2)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>85 (55.6)</td>
<td>48 (70.6)</td>
</tr>
<tr>
<td>DM (%)</td>
<td>40 (26.1)</td>
<td>25 (36.8)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>63 (41.2)</td>
<td>27 (39.7)</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>63 (41.2)</td>
<td>43 (63.2)</td>
</tr>
<tr>
<td>Mean daily doses of</td>
<td>DONEP, mg (SD)</td>
<td>7.3 (4.6)</td>
</tr>
<tr>
<td></td>
<td>GALAN, mg (SD)</td>
<td>1.5 (4.9)</td>
</tr>
<tr>
<td></td>
<td>RST, mg (SD)</td>
<td>0.5 (1.9)</td>
</tr>
<tr>
<td></td>
<td>MEMA, mg (SD)</td>
<td>2.5 (6.1)</td>
</tr>
</tbody>
</table>

BMI = body mass index, CVD = cardiovascular disease, DM = diabetes mellitus, SD = standard deviation.
A more selective α1-adrenergic antagonist is the primary therapy for patients with BPH presenting with lower urinary tract symptoms, particularly in the elderly, and they are used by 80% of physicians as the first-line agent to treat this common condition in aging males. Four common α1-adrenergic antagonists are recommended by the American Urological Association for the management of lower urinary tract symptoms: tamsulosin, terazosin, doxazosin, and alfuzosin. Of these drugs, tamsulosin has been reported to have adverse effects on cognitive function through its selectivity for α1A subtype α1-adrenoceptors in the brain. In experimental studies using mice, suppressed expression of the α1A-adrenoceptors was associated with poor cognitive performance, whereas long-term stimulation of the α1A-adrenoceptors in mice improved synaptic plasticity, enhanced learning and memory, and induced anti-depressant-like behavior that was reversed by the administration of an α1A-adrenoceptor blocker. Clinical studies have also reported conflicting findings regarding the association between the use of tamsulosin and clinical onset of AD dementia. In addition, several studies have shown that tamsulosin crosses the blood-brain barrier (BBB) and at least 1 human study has reported decreased expression of α1A-adrenoceptors in the prefrontal cortex of dementia patients. Conversely, several studies have demonstrated that tamsulosin does not cross the BBB. Therefore, to resolve this conflict, experimental studies should explore the pathophysiological mechanisms and impacts of tamsulosin in the brain on cognition.

Typical late-onset AD is likely to be driven by a complex interplay between genetic and environmental factors that develop over decades. It is now thought that ~70% of AD risk is attributable to genetic factors. The pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia. Emerging evidence from both genetic at-risk and aging cohorts suggests that there is a time lag of a decade or more between the beginning of the pathological cascade of AD and the onset of clinically evident impairment. The associations observed in previous studies were over relatively short median times, which were probably too short to cause dementia. It is possible that tamsulosin just unmask symptoms in patients who already have preclinical or early AD, rather than actually causing it. Thus, we investigated the effect of tamsulosin on worsening of cognition in patients with mild or moderate AD, unlike the previous study.

We used the MMSE as a cognitive assessment. Using the MMSE, the cognitive decline in AD patients was found to range from a loss of 2.7 to 4.5 points annually. Receiving drug therapy for AD, such as an AChEI or memantine, can reduce the rate of cognitive decline. In a retrospective study with 92% to 95% of the patients receiving drug treatment, the overall MMSE decreased annually by 0.83 ± 2.13 points during a 2.4 ± 1.3-year follow-up period. Another study showed that the mean difference in the MMSE score from baseline was −0.6 (−0.3 to −0.8) after 1 year of AChEI treatment, −2.3 (−1.9 to −2.7) after 2 years, and −3.2 (−2.7 to −3.7) after 3 years. Similar to previous findings, in our study with all patients receiving medication for dementia, such as AChEI or memantine, the annual decline in MMSE score was 0.98 and 0.75 in the tamsulosin and no-medication groups, respectively.

The rate of cognitive deterioration during the course of AD varies markedly across individuals, and is driven by various clinical factors. Although some studies suggest that sociodemographic and clinical factors, such as younger age, higher education, undernutrition, and vascular risk factors, such as hypertension, diabetes, hypercholesterolemia, aggravate the cognitive decline in AD, other reports do not support these findings. Cognitive test results at baseline and an MMSE score <20 at treatment onset were also associated with rapid cognitive decline in AD. Thus, we analyzed the clinical factors that may influence cognitive decline during the course of AD. There were no significant differences in age, educational attainment, BMI, or vascular risk factors, such as the proportions with hypertension, diabetes, and hypercholesterolemia, across the groups in our study. The baseline MMSE scores did not differ significantly between the tamsulosin and no-medication groups. However, cognitive decline during the course of AD is also likely to be driven by genetic factors. One study reported that carriers of the apolipoprotein E (APOE) ε4 allele undergo accelerated cognitive decline due to the allele’s cumulative impact on the beta amyloid and neurofibrillary tangle biochemical pathways. We lacked genotype information for the patients with AD. However, this hypothesis has been explored for >10 years with no resolution and the studies directly examining decline as a function of APOE genotype have produced inconsistent findings.

This study has several limitations. First, it used data collected from individuals who visited a single university hospital in a regional community and is also limited by the small number of subjects. Therefore, it is difficult to generalize the results to the general population, and the possibility of selection bias must be considered. Next, our study was retrospective and we did not have detailed clinical data including genetic information, such as the APOE genotype. Future studies should examine the association between the use of alpha-blockers as a treatment for BPH and aggravation of dementia in broader patient populations with long-term follow-up.

### 5. Conclusion

In conclusion, this study examined possible associations between the use of tamsulosin and cognitive decline in males with mild to moderate AD. After propensity score matching for clinical factors influencing cognition, the MMSE scores obtained >1000 days apart did not differ significantly between the tamsulosin and no-medication groups. These findings suggest that tamsulosin is not associated with cognitive decline in patients with AD. Future prospective, population-based studies are needed to investigate the association between the use of tamsulosin and its impact on cognition or dementia risk.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin group</th>
<th>No med. group</th>
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<tbody>
<tr>
<td>Baseline MMSE</td>
<td>19.0 ± 5.8</td>
<td>19.6 ± 5.9</td>
</tr>
<tr>
<td>Follow-up MMSE</td>
<td>15.4 ± 7.1</td>
<td>16.9 ± 7.3</td>
</tr>
<tr>
<td>MMSE difference</td>
<td>3.6 ± 6.0</td>
<td>2.8 ± 6.8</td>
</tr>
<tr>
<td>MMSE interval</td>
<td>1341.2 ± 165.4</td>
<td>1362.0 ± 231.9</td>
</tr>
</tbody>
</table>

**Note:** MMSE = Mini-Mental State Examination, SD = standard deviation.
Author contributions
Jong-Hee Sohn contributed to this work as first authors. Jae Jun Lee and Youngmi Kim equally contributed as the corresponding author.
Sang-Hwa Lee helped acquisition and interpretation of data. Young-Suk Kwon helped acquisition and analysis of data. Jong-Ho Kim helped acquisition and analysis of data.
Jae Jun Lee and Youngmi Kim helped study supervision and revising paper.

References
